PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

Pilkington, Stephanie
ERIC POTTER CLARKSON
Park View House
58 The Ropewalk
Nottingham
Nottinghamshire NG1 5DD
GRANDE BRETAGNE

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(PCT Rule 71.1)

Date of mailing *(day/month/year)*	23.08.2005
Applicant's or agent's file reference MEDBY/P31555PC	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB2004/004060	27.09.2004	27.09.2003

Applicant
MEDICAL RESEARCH COUNCILet al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary report on patentability and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary report on patentability. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international preliminary examining authority:

European Patent Office - P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk - Pays Bas
Tel. +31 70 340 - 2040 Tx: 31 651 epo nl
Fax: +31 70 340 - 3016

Authorized Officer

Wallentin, M

Tel. +31 70 340-3991

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference MEDBY/P31555PC	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/GB2004/004060	International filing date *(day/month/year)* 27.09.2004	Priority date *(day/month/year)* 27.09.2003

International Patent Classification (IPC) or national classification and IPC
G01N33/50, A61P35/00, A61P9/10, A61P3/10, A61P25/00

Applicant
MEDICAL RESEARCH COUNCILet al.

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 8 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 2 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
21.07.2005	23.08.2005

Name and mailing address of the international preliminary examining authority:
European Patent Office - P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk - Pays Bas
Tel. +31 70 340 - 2040 Tx: 31 651 epo nl
Fax: +31 70 340 - 3016

Authorized Officer
Vanhalst, K
Telephone No. +31 70 340-3075

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/GB2004/004060

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1-73	as originally filed

Claims, Numbers

1-13	as originally filed
14-17	received on 21.07.2005 with letter of 21.07.2005

Drawings, Sheets

1/11-11/11	as originally filed

☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-6,8,10,12,14-17 (partially)

because:

☒ the said international application, or the said claims Nos. 1-6,8,10,12,16,17 (partially) relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 14,15 (partially) are so unclear that no meaningful opinion could be formed *(specify)*:

see separate sheet

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-6,9-11,14-17
	No:	Claims	7,8,12,13
Inventive step (IS)	Yes:	Claims	1-6,9-11,14-17
	No:	Claims	7,8,12,13
Industrial applicability (IA)	Yes:	Claims	7,9,11,13-15
	No:	Claims	1-6,8,10,12,16,17

2. Citations and explanations (Rule 70.7):

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1 In accordance with Rule 66.1(e) PCT, the written opinion with regard to novelty, inventive step and industrial applicability is restricted to the subject-matter that was searched, as outlined below:

1.1 The subject-matter of claims 1-6,8,10 and 12 partially relates to methods of treatment, performed on the human or animal body and is therefore considered by this search authority to be covered by the provisions of Rule 67(iv) PCT. The Search has been restricted to those parts of the subject-matter relating to in-vitro methods.

1.2 The subject-matter of claims 16 and 17 relates to methods of treatment, performed on the human or animal body and is therefore considered by this search authority to be covered by the provisions of Rule 67(iv) PCT. The search has been limited to the alleged effects of the compounds used.

1.3 Present claims 14 and 15 relate to a compound defined by reference to a desirable characteristic or property, namely being able to modulate the interaction between PIP2 and TAPP. The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compound by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the siRNA-compounds mentioned in the description at pages 56 and 62-63.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1 **Amendments** (Art. 41(2) PCT)

1.1 The amendments of claims 14-17 fulfil the requirements of Article 41(2) PCT, since they now state only one of the multiple preferred embodiments of the original application, thereby limiting the scope of the claims without adding subject-matter not originally disclosed.

2 **Cited documents**

2.1 Reference is made to the following documents, the numbering will be adhered to throughout the examination procedure.

D1: BOMPARD GUILLAUME ET AL: "Membrane targeting of protein tyrosine phosphatase PTPL1 through its FERM domain via binding to phosphatidylinositol 4,5-biphosphate." JOURNAL OF CELL SCIENCE, vol. 116, no. 12, 15 June 2003 (2003-06-15), pages 2519-2530, XP002319141 ISSN: 0021-9533

D2: WO 02/12276 A (MEDICAL RESEARCH COUNCIL; DOWLER, SIMON; CAMPBELL, DAVID; GRAY, ALEXAN) 14 February 2002 (2002-02-14)

D3: US-A-5 821 075 (GONEZ ET AL) 13 October 1998 (1998-10-13)

2 **Novelty** (Art. 33(2) PCT)

2.1 None of the cited documents disclose the combination of features as stated in independent claims 1, 9, 10, 14, 16 and 17. The subject-matter of claims 1, 9, 10 and their dependent claims 2-6, 11 and 15 is therefore new and fulfils the requirements of

Article 33(2) PCT.

2.2 D1 discloses (the references in parentheses refer to this document):

2.2.1 A method for selecting a compound for modulating signalling via PIP2, comprising the step of identifying a compound that modulates the intracellular localisation of PTPL1, as in claim 7, and exposing the PTPL1 polypeptide to the compound, as in claims 8, 12 and 13. (D1 discloses the effect of neomycin (a compound) on the intracellular localisation of PTPL1 due to perturbation of the interaction between PTPL1 and PIP2, thereby implicitly disclosing a method to select such a compound (neomycin) cf. p2526, col.1, lines 1-26).

2.3 The subject-matter of claims 7, 8, 12 and 13 is not new and the application does therefore not fulfil the requirements of Article 33(2) PCT.

3 **Inventive step** (Art. 33(3) PCT)

3.1 D3 discloses (abstract; claims 1-12) a method for identifying compounds for modulating the cellular activity or location of PTPL1, from which the subject-matter of claim 1 differs in that the binding properties or cellular localisation of TAPP are analysed. It is at present not clear whether this difference in analysis method could result in an unexpected technical effect.

3.1.1 The objective problem can therefore be regarded as "How to provide an alternative method for identifying compounds for modulating the cellular activity or location of PTPL1?", the solution being the analysis of the binding properties or cellular localisation of TAPP.

3.1.2 D3 discloses (abstract; claims 1-12) a method that is largely similar to the one claimed in the present application, analysing the PTPL1 directly instead of looking

at the TAPP protein and its effect on the PTPL1 pathway. The use of TAPP can therefore be seen as a selection out of several members of the PTPL1 pathway. However, since the present application is the first to report on the existence of a functional interaction between TAPP and PTPL1, it can not be assumed that the person skilled in the art would consider the use of the TAPP protein in the method of D1. The choice of TAPP protein is therefore not obvious and involves inventive skills.

3.1.3 The subject-matter of claim 1 and its dependent claims 2-6, can therefore be considered to have an inventive step and fulfils the requirements of Article 33(3) PCT.

3.1.4 The same reasoning can be repeated for claims 9-11 and 14-17, because they are all founded on the functional relationship between PTPL1 and TAPP, unknown in the prior art.

3.1.5 Claims 9-11 and 14-17 are therefore also inventive and fulfil the requirements of Article 33(3) PCT.

4 **Industrial applicability** (Art. 33(4) PCT)

4.1 The subject-matter of claims 1-6,8,10,12,16 and 17 (partially) relates to methods of treatment, performed on the human or animal body and is therefore considered by this search authority to be covered by the provisions of Rule 67(iv) PCT. Since there is no consensus between the different International Search Authorities on the possible patentability of such subject-matter, no opinion on industrial applicability of these claims can be given.

4.2 The remaining claims 7,9,11,13-15 are industrially applicable and fulfil the requirements of Article 33(4) PCT.

11. The method of claim 10 performed *in vitro*.

12. A method for modulating signalling *via* PtdIns(3,4)P_2, the method comprising the step of exposing the PTPL1 to a compound which modulates the interaction between TAPP and PTPL1 or the intracellular location of PTPL1.

13. The method of claim 12 performed *in vitro*.

14. The use of a compound that ~~inhibits the interaction of PtdIns(3,4)P_2 with TAPP or that~~ inhibits the interaction of TAPP with PTPL1 in the manufacture of a medicament for treating diabetes, inhibition of apoptosis, treatment of ischaemic disease, wound healing or nerve regeneration.

15. The use of a compound that ~~promotes the interaction of TAPP with PtdIns(3,4)P_2 or that mimics the effect of PtdIns(3,4)P_2 on TAPP, or that~~ promotes the interaction of TAPP with PTPL1 in the manufacture of a medicament useful in promoting apoptosis, for example in treating cancer or in the resolution of inflammation.

16. A method of treating a patient with diabetes or in need of inhibition of apoptosis, for example in the treatment of ischaemic disease, wound healing or nerve regeneration, wherein the patient is administered an effective amount of a compound that ~~inhibits the interaction of PtdIns(3,4)P_2 with TAPP or that~~ inhibits the interaction of TAPP with PTPL1.

17. A method of treating a patient in need of promotion of apoptosis, for example in treating cancer or in the resolution of inflammation, wherein the patient is administered an effective amount of a compound that ~~promotes the interaction of TAPP with PtdIns(3,4)P_2 or that mimics the effect of PtdIns(3,4)P_2 on TAPP, or that~~ promotes the interaction of TAPP with PTPL1.